

Exercise 1

1. Go to the MapViewer web site
2. Click “Homo sapiens (human)...” (the latest Build)
3. Since the microsatellite name is D14S... you know that the chromosome you have to investigate is chromosome 14. Click then on the Chr 14 link
4. Type rs4899655 OR D14S905 in the Search window and click “Find in this view”
5. Zoom on the region containing the 2 red dots, for example by typing 75M and 77M in the “Region shown” window
6. Look at the genes that are in the region and investigate them. There are a few good candidates. Neuroglobin and POMT2 are among them.

Exercise 2

1. Go to the NCBI BLAST website (<http://www.ncbi.nlm.nih.gov/BLAST/>), and click “Align two sequences using BLAST (bl2seq)”
2. In the Sequence 1 window, type NM_000492.3, in the Sequence 2 window, cut and paste the sequence provided
3. BLAST2 tells you immediately that you have aligned the CFTR mRNA, so you don’t have to find out what gene this is
4. Note that the “identities” are not 100%, so there must be at least one difference between the 2 sequences. Find this difference by carefully scrolling down the alignment (if you really cannot see the difference by eye, try CTRL+F or APPLE+ F with “|”)
5. Once you find it, go to the CFTR web page in ENSEMBL, and click “Transcript info”
6. Make sure that “Exon, Codons, Translation, SNPs and Coding sequence” are selected
7. With CTRL+F or APPLE+F find the region where the discrepancy was detected by BLAST2.
8. Count what codon (aa residue) this is (specifically, this is Q493) and, with a genetic code table, what does this nucleotide change do to the codon. In this case, a Q (Gln) codon is transformed in X (End, or Ter), so the change is Q493X, or Gln 493Ter, or Gln493End
9. Since this change is not reported in ENSEMBL (colored bases and/or residues, see the legend at the bottom of this page), it is likely (although not certain) that this is not a polymorphism
10. To find out whether this is a mutation, go to the OMIM web site and look for CFTR. Then find whether Q493X has been described already (in this case, it has, so this is really a mutation)
11. IMPORTANT. In case you did not find Q493X in OMIM and in any other mutation databases, the only way to know whether this change is pathogenic or not (mutation or not) would be to determine it experimentally. To address the question whether this is a benign rare variant or polymorphism, you would have needed to have more information about this change in the general population. Therefore, in case you could not classify Q493X as a mutation, the

information provided in the exercise was insufficient to make you decide whether it was a rare variant or a polymorphism.